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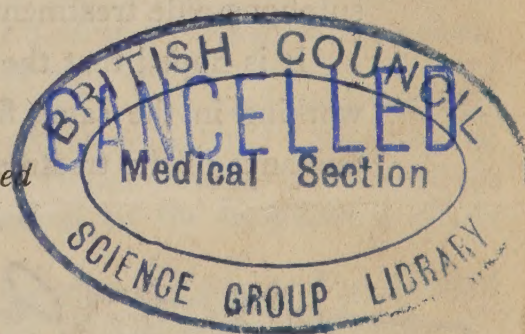


DEPARTMENT OF HEALTH
FOR SCOTLAND

SULPHONAMIDES IN THE TREATMENT OF MENINGOCOCCAL MENINGITIS

Report to the
SCIENTIFIC ADVISORY COMMITTEE

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FOREWORD

THE increase in the incidence of meningococcal meningitis during the early part of 1940 gave rise to some anxiety but it also gave an opportunity of appraising the efficacy of some of the new sulphonamide drugs in the treatment of this infection. These drugs had been dramatically successful in many infectious diseases, and even in meningococcal meningitis it was known that they effectively reduced the fatality rate. But new and improved forms of sulphonamide made their appearance in the therapeutic world in such rapid succession that it became difficult to keep abreast of the new discoveries or, at any rate, to test accurately their effects. The Memorandum of the Medical Research Council on the "Use of Sulphonamides" was a timely and authentic publication on the subject, for there is a general feeling among experts that this form of therapy is in danger of being misused, even abused.

This Report is an attempt to evaluate the relative efficiency of some of the best known members of the group in the treatment of meningococcal meningitis. Certain hospitals were chosen for the enquiry, and the Report includes an analysis of all the cases accepted by these hospitals from the 1st January 1936. Sulphonamide therapy had scarcely been applied before 1938 so that it is possible to compare results of treatment in the pre-sulphonamide days with those when sulphonamide treatment was available.

It is hoped that the results of this enquiry will be helpful to those working in the same field and that they may possibly be of general guidance in the treatment of this dangerous infectious disease.

Andrew Davidson

CHIEF MEDICAL OFFICER,
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SULPHONAMIDES IN THE TREATMENT OF MENINGOCOCCAL MENINGITIS

PRELIMINARY REPORT TO THE SCIENTIFIC ADVISORY COMMITTEE
TO THE DEPARTMENT OF HEALTH FOR SCOTLAND

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Introductory

SCOPE OF THE SURVEY

EARLY in 1940, when it was evident that an exceptionally large epidemic of cerebro-spinal fever was occurring in Great Britain, the Infectious Diseases Sub-Committee of the Scientific Advisory Committee to the Department of Health for Scotland considered that the opportunity presented itself for a detailed assessment of the recent history of the disease in Scotland, especially in view of the advances in treatment. A working sub-committee was formed, and the decision made that every case from the beginning of 1936 to the end of 1941, admitted to and accepted by the infectious disease hospitals of Edinburgh, Glasgow (Belvidere, Knightswood and Ruchill), Dundee, Aberdeen City and Lanark County (County Hospital) should be summarised on an agreed record card; 2223 cards, representing all accepted cases in the participating hospitals, have been completed. The records are of about 40 per cent. of all cases (civilian and service) notified in Scotland in 1936-41. The population of the areas directly served by the hospitals is about 45 per cent. of the population of Scotland.

Each patient's record started with the usual data on admission and proceeded through diagnostic puncture, blood culture, details of treatment with antitoxin, serum, sulphonamide compounds, parenteral fluids, etc., to drug concentrations, drug intolerances, duration of primary pyrexia, complications, number of days in hospital, result and post-mortem findings; with some subsidiary data. Some of these procedures or investigations had been carried out only in certain hospitals. On careful consideration, it was decided not to attempt a grading of clinical severity on admission, but rather to try to assess, by the results, the relative weights of more measurable factors in determining prognosis. Through facilities generously provided by the Department of Health for Scotland, the original data were coded and transferred to punched cards for machine tabulation.

So considerable is the total information that the Sub-committee have decided

to summarise and discuss some of the results in this preliminary report ; it is hoped to publish a more detailed report later. Meantime, this report gives a simpler, possibly clearer, picture of the disease during the six years studied. To conform to a now common practice, deaths within 24 hours of admission have been separated from those 24 hours or more after admission, which gives a rough indication of those patients who died before they could receive the full benefit of specialised treatment (which included few sulphonamide drugs in the first two years of the survey). A deliberate selection has been made of the criteria by which the cases have been judged in this first report.

Historical

RECORDS FOR FORTY YEARS

The recorded history of cerebro-spinal fever in Scotland goes back about forty years. Many Local Authorities made the disease notifiable in their areas from 1905 onwards, though notification was not enforced by legislation until 1933. During the period 1906-14, the then Local Government Board ran a concurrent system of "intimation" which provided more detailed information than did the notification returns. Notified cases have shown four peaks, with maxima of 2115 in 1907, 409 in 1915 and 1931, and 2580 in 1940. The decline after each maximum has been slow, taking three years or so to reach inter-epidemic level. Judgment of this level is complicated by the fact that the inter-epidemic prevalence has been steadily increasing ; whereas there were, on the average, only 70 notifications yearly in 1911-14, there were never less than 200 yearly in 1929-39. Reasons for the trend are not sought in this summary, though several will suggest themselves.

The secular changes in notifications can be further studied by data derived from the weekly returns of infectious disease. These returns do not give as complete information as is desirable over the whole period, having been started in 1923 for the larger areas only and extended to the whole country in 1930. For the period 1923-42, the first quarters accounted for 32.4 per cent. of annual notifications ; the succeeding quarters providing 30.7, 19.0 and 17.9 per cent. respectively. Individual weeks in the period 1931-39 gave a highest median value of 14 in the second week of the year, and a lowest median of 4 in the forty-first week of the year. The age groups of notified cases are available for 1912-41. Of 10,532 notifications, 2005 (19.0 per cent.) were under 1, 4742 (44.9 per cent.) under 5, 6972 (66.0 per cent.) under 15, and 10,477 (99.3 per cent.) under 65. Subdivisions of these total figures into rural and urban areas and into years of high and lower prevalence show differences which need not be detailed here, except to mention that the burgh totals for this period show an even greater preponderance of infants and young persons, the percentages in the above age groups being 23.0, 50.1, 69.3 and 99.4. This contrast is given only as a rough guide, as the number of burghs included in the totals underwent a large change in 1930. Contrast may also be made with the 45.5 per cent. of patients under 15 in the recent English survey of hospital cases (Beeson and Westerman, 1943).

It is not intended to discuss mortality in detail. Information similar to that outlined for notifications is available, with the further advantages that sex is entered in the death returns and that fineness of age grouping, continuity, and completeness of records are greater. Nominal fatality rates can be calculated from notifications and deaths, but confidence in their accuracy cannot be great, at least for earlier years, when it is appreciated that deaths exceeded notifications in 1912, 1913 and 1920. The "intimated" cases in 1907-14 had a fatality rate of 76.7 per cent. Certified deaths, as a percentage of notifications, showed the following change in the decade 1932-41 : 59.6 per cent., 56.9 per cent., 56.2 per cent., 49.0 per cent., 52.5 per cent., 50.3 per cent., 34.1 per cent., 20.1 per cent., 18.7 per cent., 17.8 per cent. The change in 1938 is evident.

Taking the years 1907, 1908 and 1912-37, which precede this change in nominal fatality rates, the "intimated" cases in 1907 and 1908 were tabulated in appendix tables, by age groups, in the Annual Reports of the Local Government Board for Scotland. The combined tables show fatality rates of 90·4 per cent. at ages under 1, 85·3 per cent. at 1-5, 75·6 per cent. at 6-15 and 74·0 per cent. at 16-50. On a basis of notified cases and certified deaths in 1912-37, the fatality rates for roughly comparable age groups are 88·4 per cent. at ages under 1, 71·6 per cent. at 1-4, 57·9 per cent. at 5-14, 68·9 per cent. at 15-64 (and 91 per cent. at age 65 or over). The percentage of male deaths over the main period studied (1906-41) was 57·3, with a maximum of 67·8 per cent. in the age group 15-24 and a minimum of 52·1 in the age group 5-9.

Results : I

PERIOD AND TREATMENT

The distribution of the observed cases during the period 1935-42 was as follows :—

Year	No. of Cases	Year	No. of Cases
1935	12	1939	100
1936	99	1940	1005
1937	120	1941	763
1938	110	1942	14

(The enquiry period dates from 1936 to 1941 : the small numbers in 1935 and 1942 are entirely due to the inclusion in the records of a few cases admitted late in 1935 or early in 1942.) Those cases have been divided into seven treatment groups as shown in Table I.

TABLE I
RESULTS OF DIFFERENT METHODS OF TREATMENT IN 2223 CASES OF
MENINGOCOCCAL MENINGITIS

METHOD OF TREATMENT	TOTAL CASES	TOTAL RECOVERIES	DEATHS		FATALITY RATES		
			Under 24 hrs.	After 24 hrs.	Under 24 hrs.	After 24 hrs.	Total
Group 1 No serum or drug .	12	1	9	2	—	—	—
Group 2 Serum or Antitoxin	199	96	8	95	4·02	47·74	51·76
Group 3 Sulphanilamide .	128	116	1	11	0·78	8·59	9·37
Group 4 Sulphapyridine .	1468	1216	41	211	2·79	14·37	17·17
Group 5 Sulphathiazole .	75	64	1	10	1·3	13·3	14·6
Group 6 Miscellaneous Sulphonamides .	91	72	1	18	1·1	19·8	20·9
Group 7 Serum or Antitoxin and Sulphonamide Drugs .	250	172	6	72	2·40	28·80	31·20
A. Total (1-7) Cases .	2223	1737	67	419	3·01	18·85	21·86
B. Total (3-6) Sulphonamides only	1762	1468	44	250	2·49	14·19	16·68

The figures in the table require little explanation. In respect of fatality rate alone the best results were obtained with sulphanilamide. The numbers here are unfortunately small as this method of treatment was largely confined to one investigational centre. Two points emerge from a study of the Table. First, the fatality rate of these cases which received sulphonamides only (16·7 per cent.) represents a great improvement on the fatality rate of nearly 52 per cent. in those who received serum alone. Second, the cases which received serum or anti-toxin combined with a sulphonamide drug showed a much higher fatality rate (31 per cent.) than those who received the drugs alone. It should be emphasised that the cases in treatment groups 3, 4, 6 and 7 are well distributed in the years from 1938–42. No group shows an undue proportion of cases either at the beginning or at the end of the epidemic. (Group 5 (sulphathiazole), was, of course, used only in 1939 and 1940.) This point may be worth stressing, for if the sulpha-pyridine group is analysed in regard to the annual fatality rate, we find that the rates in 1939, 1940 and 1941 were 11·40, 16·50 and 17·88 per cent. respectively. This suggests that as the epidemic advanced the mortality rose slightly.

Results : 2

AGE AND SEX

Table II shows the distribution of the cases and deaths by age and sex. The following points emerge from a study of the Table.

(a) Cases. (i) Sex. Of the total series 55 per cent. were males. This excess of males is seen in all but two of the treatment groups, namely, sulphanilamide and sulphonamide+serum. The centre which persisted in sulphanilamide therapy received a high proportion of the adult female cases occurring in that area so that the distribution is artificial. In the group which received sulphonamides+serum there were 49 per cent. males : this difference is not statistically significant.

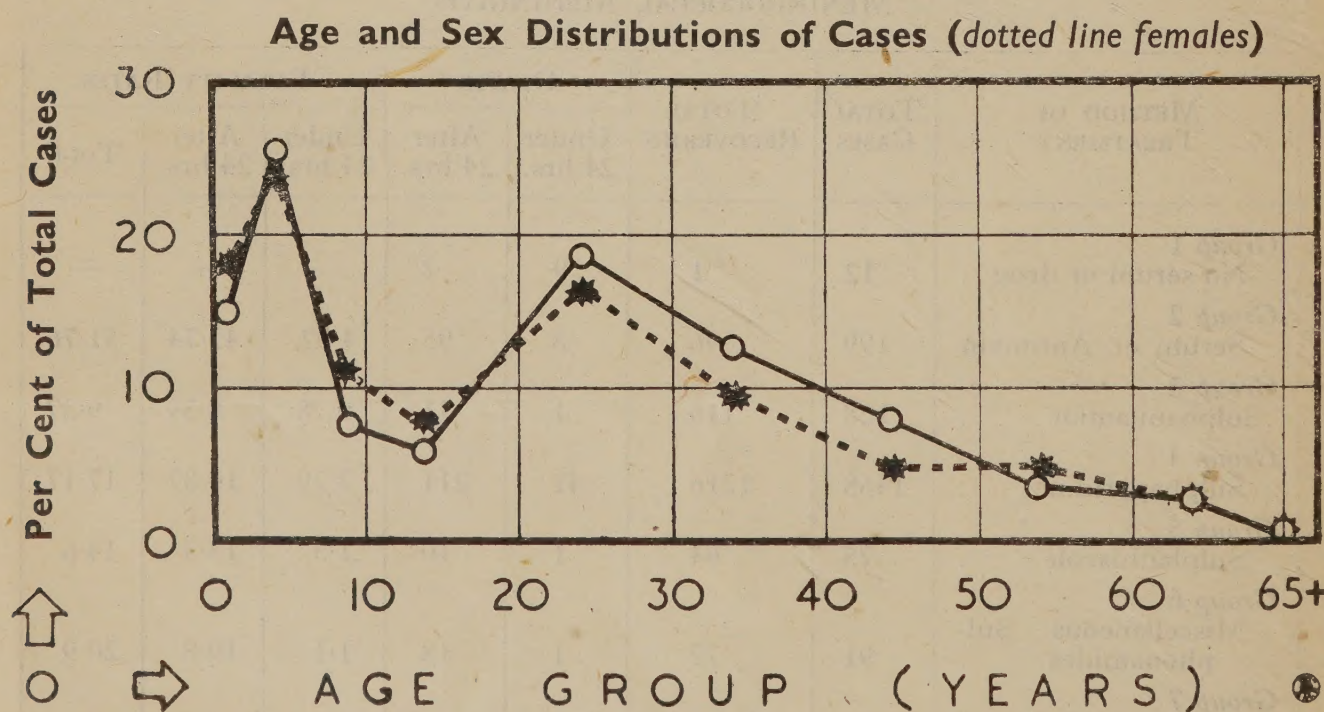


FIG. 1.

(ii) Age. The age distribution in the two sexes follows a similar pattern (Fig. 1). Thus the proportions under 5 years of age were : males—40·1 per cent. ; females—42·3 per cent. In the age group 15–24 years (in which a secondary peak of incidence occurs) the proportions were : males, 18·8 per cent. ; females, 16·8 per cent.

TABLE II

THE DISTRIBUTION OF CASES BY SEX AND AGE AND THE MORTALITY BY AGE

AGE GROUP	TOTAL SERIES			CASES WHO RECEIVED SULPHONAMIDE DRUGS ONLY			CASES WHO RECEIVED SULPHONAMIDE+SERUM			CASES WHO RECEIVED SERUM ONLY		
	CASES			CASES			CASES			CASES		
	M	F	Both Sexes	DEATHS BOTH SEXES	M	F	Both Sexes	DEATHS BOTH SEXES	M	F	Both Sexes	DEATHS BOTH SEXES
-1	207	186	393	141 (35.8)	143	137	280	79 (28.3)	26	23	49	18 (36.8)
1-4	318	261	579	139 (24.1)	253	192	445	83 (18.7)	29	44	73	24 (32.9)
5-9	97	112	209	31 (14.8)	75	84	159	17 (10.7)	14	14	28	7 (25.0)
10-14	77	77	154	17 (11.0)	58	58	116	3 (2.6)	10	9	19	6 (31.6)
15-24	221	154	375	35 (9.3)	186	130	316	19 (6.0)	20	16	36	8 (22.2)
25-34	145	88	233	24 (10.3)	126	75	201	17 (8.5)	13	8	21	2 (9.5)
35-44	90	47	137	30 (21.9)	80	37	117	18 (15.4)	8	8	16	8 (54.1)
45-54	40	41	81	35 (43.1)	34	38	72	29 (40.4)	3	1	4	2 (54.1)
55-64	26	23	49	23 (47.0)	26	20	46	21 (45.7)	0	3	3	2
65+	6	7	13	11	4	6	10	8	0	1	1	1
All Ages	1227	996	2223*	486 (21.9)	985	777	1762	294 (16.7)	123	127	250	78 (31.2)
									112	87	199	103 (51.8)

(The figures in brackets are percentages.)

* Including 12 cases, with 11 deaths, which received neither sulphonamide drugs nor serum.

(b) Deaths. (i) *Sex*. The following fatality rates were encountered in respect of sex :—

	<i>Male</i>	<i>Female</i>	<i>Difference</i>	<i>S.E.D.</i>
Total Series	22.9	20.6	2.3	± 1.76 ($P=0.19$)
Sulphonamides only	17.1	16.3	0.8	
Sulphonamides + Serum	31.8	30.7	1.1	
Serum only	59.8	41.4	18.4	± 7.14 ($P=0.01$)

These figures show that sex has no effect upon the fatality rate, except in these cases which received serum only, where the fatality rate in male cases is rather higher than among females.

(ii) *Age and Sex*. For the sulphonamide-treated group, the mortality by age and sex was studied. At no age group was the difference in fatality rate between the two sexes statistically significant (a χ^2 test showed $\chi^2=6.76$, $P=0.6$, indicating a good "fit" between the distribution of deaths in the two sexes).

(iii) *Age*. Since sex has been shown to have no effect upon the mortality the fatality rates may be computed for each age group in the combined sexes. These figures are shown in Table II and Fig. 2 for the main treatment groups. Clearly, age is of great importance in respect of outcome. For all three main treatment groups the fatality rate is high under 2 years and remains fairly high up to 5 years ; having fallen sharply it remains low throughout the middle age groups to rise again after the age of 35 years. The figures in the Table and in Fig. 2 suggest a parallelism between the rates obtained with serum alone and those obtained with sulphonamides + serum. It was thought that this might be due to the latter cases having received inadequate doses of the drugs, so that the effect was mainly a serum one. Such a possibility must be entertained, for if the cases which survived four days in hospital are allocated to three groups representing three grades of dosage of sulphonamide, during the first four days, we find that a relatively higher proportion of those who were given combined treatment received a low dosage of the drug (Table III). It may further be stated that the age-distribution of the different treatment groups is essentially similar ; and that the high fatality rate encountered among those who were given the combined treatment was not due to any inequality in the age-distribution of the cases.

TABLE III

INTENSITY OF DOSAGE WITH SULPHONAMIDES IN CERTAIN TREATMENT GROUPS

INTENSITY OF DOSAGE	SERUM+DRUG		DRUGS ALONE		SULPHAPYRIDINE ALONE	
	No.	Per-centage	No.	Per-centage	No.	Per-centage
Low dosage	127	63.2	783	52.0	648	50.2
Medium dosage	54	26.9	393	26.1	365	28.5
High dosage	20	10.0	330	21.9	271	21.2
Total	201		1506		1284	

In view of the high fatality rate found in those under the age of 5 years it is interesting to compare the results with the three main sulphonamides in this age group (Table IV, p. 10).

It is greatly to be regretted that the numbers of cases treated with sulphanilamide and sulphathiazole are so small. For what they are worth, however, the fatality

FATALITY RATES SPECIFIC FOR AGE

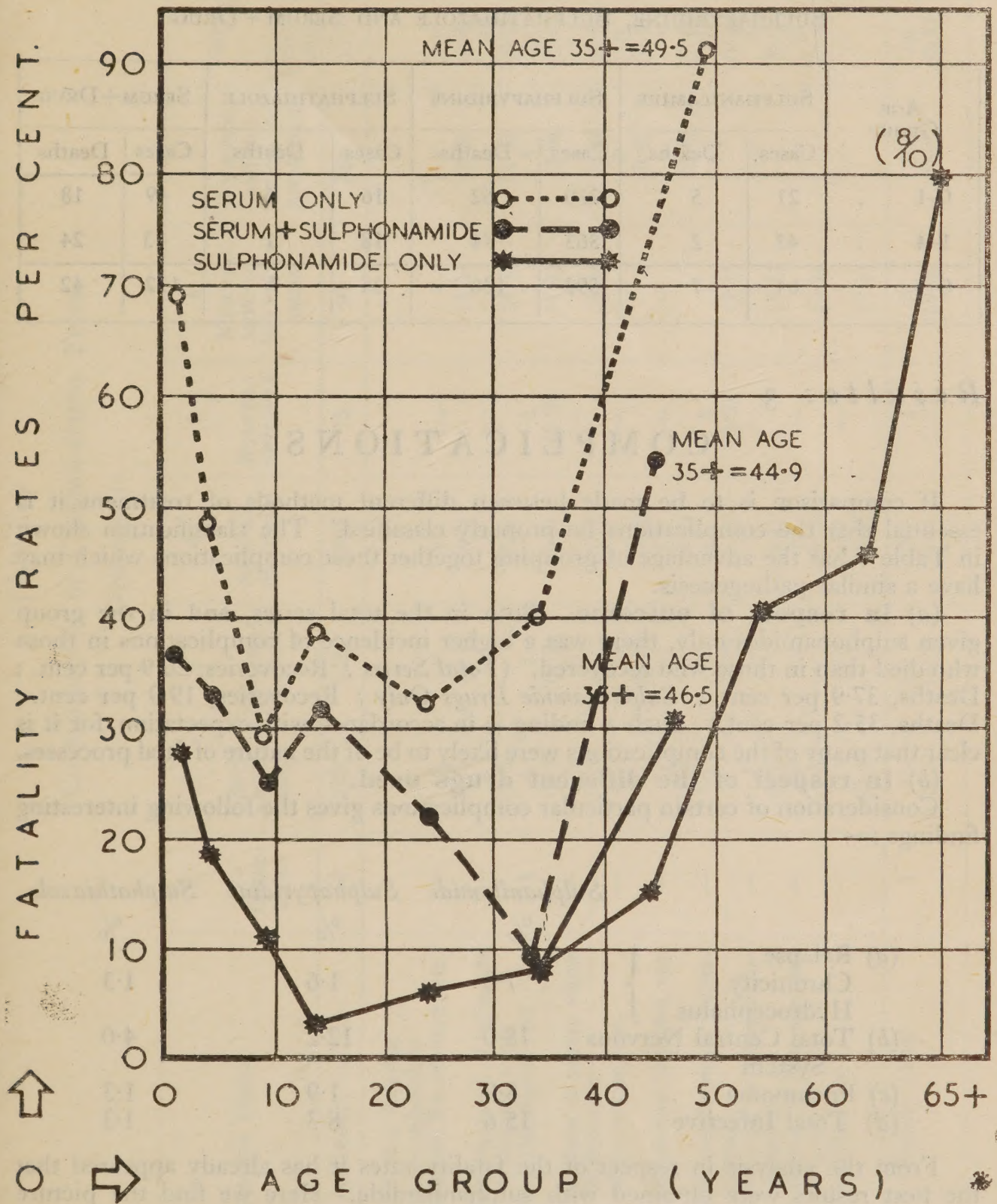


FIG. 2.

rates for the three drugs and for these given serum + drugs are : sulphanilamide, 10.93 per cent. (± 3.91) ; sulphapyridine, 22.95 per cent. (± 1.73) ; sulphathiazole, 20.6 per cent. (± 6.93) ; and serum + sulphonamides, 34.5 per cent. (± 4.31). The low rate encountered with sulphanilamide is significantly less than any of the others ; and the high rate with serum + drugs is significantly higher than any of the others.

TABLE IV

THE RESULTS OBTAINED IN CASES UNDER 5 YEARS WITH SULPHANILAMIDE, SULPHAPYRIDINE, SULPHATHIAZOLE AND SERUM + DRUG

AGE GROUP	SULPHANILAMIDE		SULPHAPYRIDINE		SULPHATHIAZOLE		SERUM + DRUG	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
0-1	21	5	230	62	16	6	49	18
1-4	43	2	363	74	18	1	73	24
0-4	64	7	593	136	34	7	122	42

Results : 3

COMPLICATIONS

If comparison is to be made between different methods of treatment it is essential that the complications be properly classified. The classification shown in Table V has the advantage of grouping together those complications which may have a similar pathogenesis.

(a) **In respect of outcome.** Both in the total series, and in the group given sulphonamides only, there was a higher incidence of complications in those who died than in those who recovered. (*Total Series* : Recoveries, 20.9 per cent. ; Deaths, 37.9 per cent. ; *Sulphonamide Drugs Only* : Recoveries, 19.9 per cent. ; Deaths, 35.2 per cent.) Such a finding is in accordance with expectation, for it is clear that many of the complications were likely to be of the nature of fatal processes.

(b) **In respect of the different drugs used.**

Consideration of certain particular complications gives the following interesting findings :—

	<i>Sulphanilamide</i>	<i>Sulphapyridine</i>	<i>Sulphathiazole</i>
	%	%	%
(a) Relapse	7.0	1.6	1.3
Chronicity			
Hydrocephalus			
(b) Total Central Nervous System	18.0	12.2	4.0
(c) Pneumonia	3.9	1.9	1.3
(d) Total Infective	15.6	8.3	1.3

From the analysis in respect of the fatality rates it has already appeared that the best results were obtained with sulphanilamide. Here we find the picture reversed : for the incidence of complications is highest with this drug.

Although the differences are not great it will be noted that all are in the same direction. In regard to relapse, etc., the inference certainly is that sulphanilamide secures a less permanent and rapid effect than either of the other drugs. The fatality rate of 16.7 per cent. in relapse suggests that relapses were dealt with as

TABLE V

COMPLICATIONS OF CEREBRO-SPINAL FEVER

DIVISION IA

TREATMENT GROUP.	1 No TREAT- MENT	2 SERUM TREAT- MENT	3 SULPHA- NILAMIDE	4 SULPHA- PYRIDINE	5 SULPHA- THIAZOLE	6 MISCELL- ANEOUS SULPHON- AMIDE	7 SULPHON- AMIDE + SERUM OR ANTITOXIN	TOTAL SERIES		TREATMENT GROUPS 3, 4, 5 and 6, <i>i.e.</i> drugs only
								Recov- eries	Deaths	R. D.
Total in Group . . .	12	199	128	1468	75	91	250	1737	486	1468 294
1. CENTRAL NERVOUS SYSTEM . . .										
(a) <i>Meningo-Encephalitic</i> —										
(i) Relapse, Recurrence, etc.	—	14 (7.0)	4 (3.1)	10 (0.7)	—	4 (4.4)	3 (1.2)	23 (1.4)	12 (2.3)	15 (1.0)
(ii) Development of subacute or chronic stage	—	3 (1.5)	—	6 (0.4)	—	4 (4.4)	3 (1.2)	3 (0.2)	13 (2.7)	3 (0.2)
(iii) Hydrocephalus, etc.	1	4 (2.0)	5 (3.9)	7 (0.5)	1 (1.3)	1 (1.1)	5 (2.0)	11 (0.7)	13 (2.7)	9 (0.6)
(iv) Blindness or severe visual disturbance	—	3 (1.5)	2 (1.6)	2 (0.1)	—	3 (3.3)	1 (0.4)	8 (0.5)	3 (0.6)	7 (0.5)
(v) Vertigo, ataxia, etc.	—	—	1 (0.8)	7 (0.5)	—	—	2 (0.8)	10 (0.6)	—	8 (0.5)
(vi) Convulsions, tremors, etc.	—	3 (1.5)	—	13 (0.9)	—	—	6 (2.4)	9 (0.6)	13 (2.7)	5 (0.3)
(vii) Hyperaesthesia or hyper- aesthesia	—	—	1 (0.8)	17 (1.2)	1 (1.3)	1 (1.1)	—	20 (1.2)	—	20 (1.4)
(viii) Emotional or mental dis- turbance	—	1 (0.5)	—	1 (0.1)	—	1 (1.1)	—	3 (0.2)	—	2 (0.1)
(ix) Retention or incontinence of urine	—	4 (2.0)	—	10 (0.7)	—	3 (3.3)	—	9 (0.6)	8 (1.7)	9 (0.6)
(x) Miscellaneous . . .	—	1 (0.5)	—	6 (0.4)	—	1 (1.1)	—	—	8 (1.7)	—
Group Total . . .	1	33 (16.5)	13 (10.2)	79 (5.5)	2 (2.7)	18 (19.8)	20 (8.0)	96 (5.5)	70 (14.4)	78 (5.3)
										34 (11.6)

DIVISION IB

TREATMENT GROUP	1	2	3	4	5	6	7	TOTAL SERIES		GROUPS 3, 4, 5 AND 6	
								Rec.	Deaths	R.	D.
1. (b) <i>Lesions of Peripheral or Cranial Nerves</i>											
(i) Ocular palsies, diplopia, etc. .	—	3 (1.5)	5 (3.9)	37 (2.5)	—	2 (2.2)	12 (4.8)	44	15	37	7
(ii) Deafness	—	2 (1.6)	2 (1.6)	21 (1.4)	—	1 (1.1)	3 (1.2)	29	—	24	—
(iii) Facial paralysis	—	—	3 (2.3)	11 (0.8)	—	—	4 (1.6)	15	3	12	2
(iv) Pharyngeal paralysis	—	—	—	—	—	—	1 (0.4)	1	—	—	—
(v) Peripheral nerve palsies	—	—	—	20 (1.4)	1 (1.3)	1 (1.1)	1 (0.4)	23	—	22	—
(vi) Severe muscle stiffness	—	—	—	9 (0.6)	—	—	—	9	—	9	—
Group Total	—	5 (2.5)	10 (7.8)	98 (6.7)	1 (1.3)	4 (4.4)	20 (8.4)	121 (7.0)	18 (3.7)	104 (7.1)	9 (3.1)

DIVISION II, (a) AND (b)

	1	2	3	4	5	6	7	TOTAL SERIES		GROUPS 3, 4, 5 AND 6	
								Rec.	Deaths	R.	D.
2. Complications due to presence of Inflammation											
(a) Infective Process											
(i) Ocular, e.g. corneal ulcers, uveitis, etc.	—	1	2	6	—	—	8	14	3	8	—
(ii) Aural, e.g. otitis media, etc.	—	4	1	15	—	1	1	19	3	15	2
(iii) Oro Nasal, e.g. stomatitis, etc.	—	3	2	2	—	1	—	5	3	4	1
(iv) Pulmonary System, bronchitis	—	3	2	13	—	—	1	13	5	11	4
pneumonia	1	(1.5)	(1.6)	(0.9)	—	—	(0.4)	(0.7)	(1.0)	(0.7)	(1.4)
		7	5	28	1	2	15	15	44	10	26
		(3.5)	(3.9)	(1.9)	(1.3)	(2.2)	(6.0)	(0.9)	(9.1)	(0.7)	(8.9)
(v) Renal Tract, e.g. cystitis, pyelitis, etc.	—	—	—	6	—	—	—	6	—	6	—
(vi) Gastro Intestinal Tract, e.g. gastro enteritis, etc.	—	1	5	23	—	—	4	18	15	14	14
(vii) Skin, e.g. furunculosis, etc.	—	3	1	2	—	—	2	6	2	3	—
(viii) Joints, arthritis	—	1	2	26	—	2	6	37	—	30	—
		(0.5)		(1.8)		(2.2)	(2.4)	(2.1)		(2.0)	
Group Total	—	25	20	121	1	6	37	133	75	101	47
		(12.6)	(15.6)	(8.3)	(1.3)	(6.6)	(14.4)	(7.7)	(15.4)	(6.9)	(16.0)
(b) Toxic											
e.g. nephritis, myocarditis, haemorrhage	—	3	—	78	—	4	8	12	21	9	13
								(0.7)	(4.4)	(0.6)	(4.5)

(The figures in brackets are percentages)

successfully as primary infections. Perhaps of more immediate importance, however, is the finding that pneumonia occurred more frequently in the group treated with sulphanilamide. It will be noted that pneumonia was a complication in 9 per cent. of the deaths. This is a high rate. The bacterial cause of the pneumonia is not known : but it might be expected that in many of them a pneumococcus was the responsible organism. The poverty of effect of sulphanilamide against this organism might suggest that a sulphonamide with a wider range of activity has a value in preventing the occurrence of what may frequently prove a fatal complication.

Results : 4

ILLNESS PRIOR TO ADMISSION

The duration of illness before the institution of chemotherapy appears to be of secondary importance if the delay has not exceeded one week. In the group of cases treated with chemotherapy alone there was actually a greater mortality among those admitted in the first few days of the illness than in those admitted in the latter part of the first week (Table VI). The greater likelihood of more severe cases being diagnosed at an early stage probably accounts for this, for to a lesser degree the same thing is manifest in those cases treated by serum alone and by combined serum and chemotherapy. In the chemotherapy group the mortality within 24 hours of admission was greatest in those admitted early in the disease. It is interesting, however, to note the difference between individual members of this group. Of 1414 * cases treated with sulphapyridine, 39 (2·7 per cent.) died within 24 hours of admission, 29 of these having been ill for 3 days or less. Of a total of 122 cases treated with sulphanilamide only one (0·8 per cent.) died within 24 hours of admission, this case being 11 days ill when admitted, while in 72 cases where sulphathiazole was used there was again only one death (1·4 per cent.), the case on admission having been ill for 5 days. This finding is nevertheless quite consistent with our opinion that prompt diagnosis with the early application of chemotherapy must always remain of the utmost importance.

Results : 5

STAY IN HOSPITAL

Although these results are compiled from the records of a number of hospitals with different administrative systems and possibly different standards of fitness for discharge of patients, they nevertheless afford a rough measure of the time taken to restore a patient to normal. In all hospitals the clinical condition of the patient was the deciding factor as to discharge ; in no case was bacteriological proof of freedom from infectivity sought.

Taking the sulphonamide groups as a whole, employment of these substances has made a remarkable reduction in the duration of stay in hospital. It will be noted that the treatment of approximately 70 per cent. of the sulphapyridine and miscellaneous sulphonamide groups was completed in 29 days or less and approximately 76 and 89 per cent. of the sulphanilamide and sulphathiazole groups in the same time. Compared with serum-treated cases, in which the treatment of 49 per cent. was not terminated in 50 days or over, the therapeutic advantage in the sulphonamide group is brought out very clearly. Again compared with the sulphonamides the combined serum and chemotherapy results are most disappointing (Table VII, p. 16).

* This, and subsequent figures in this and the following paragraphs, exclude cases where the duration was unstated.

TABLE VI

DURATION OF ILLNESS IN DAYS BEFORE ADMISSION

TYPE OF SPECIFIC TREATMENT		DURATION OF ILLNESS IN DAYS BEFORE ADMISSION									
		0	1	2	3	4	5	6	7	8	9+
SERUM alone	Total Cases	3	17	16	33	26	15	14	12	11	49
	Percentage Mortality under 24 hrs.	—	—	6	6	4	13	—	8	—	—
	Percentage Mortality after 24 hrs.	67	47	56	42	46	47	36	25	73	55
SERUM and CHEMOTHERAPY	Total Cases	—	17	56	53	38	25	11	14	7	23
	Percentage Mortality under 24 hrs.	—	6	4	6	—	—	—	—	—	—
	Percentage Mortality after 24 hrs.	—	29	29	19	26	32	—	43	43	43
CHEMOTHERAPY alone	Total Cases	26	217	418	332	235	150	94	51	36	137
	Percentage Mortality under 24 hrs.	—	4	4	2	1	2	2	—	3	2
	Percentage Mortality after 24 hrs.	15	12	14	18	9	11	11	20	8	20

The comparative periods of stay in hospital as between the various drugs employed are of some interest. The best results are those obtained by sulphathiazole, the number treated by which, however, is not great. As has been pointed out this drug was employed in 1939 and 1940, so it cannot be said that the epidemic was on the wane with a greater proportion of less severe cases. Apart from its specific effect possibly the main factor in producing the shortest stay in hospital is its relatively lower toxicity, which renders it more tolerable to the patient. Sulphanilamide is the next most favourable drug, this bearing out the good impression derived from the case fatality rate previously noted. It has been claimed that sulphapyridine is not only a more potent drug in the treatment of cerebro-spinal fever, but also exerts a more rapid action than sulphanilamide. This is not borne out by these figures which show that approximately 76 per cent. of the sulphanilamide patients had been discharged at the end of 29 days as compared with 71 per cent. of the sulphapyridine patients at the end of that time.

TABLE VII
DURATION OF STAY IN HOSPITAL

TYPE OF TREATMENT	29 DAYS OR LESS	30-49 DAYS	50+ DAYS
Serum (or Antitoxin) (96 cases)	6.2 per cent.	44.8 per cent.	49 per cent.
Sulphanilamide (116 cases)	75.85 per cent.	18.97 per cent.	5.17 per cent.
Sulphapyridine (1216 cases)	70.55 per cent.	24.67 per cent.	4.77 per cent.
Sulphathiazole (64 cases)	89.1 per cent.	7.8 per cent.	3.1 per cent.
Miscellaneous Sulphonamides (72 cases)	70.8 per cent.	13.9 per cent.	15.3 per cent.
Combined serum and Chemotherapy (172 cases)	36.04 per cent.	46.52 per cent.	17.44 per cent.

Results : 6

DOSAGE OF DRUG

This is perhaps the most difficult subject to analyse satisfactorily. In order to permit as accurate a comparison as possible the figures for sulphapyridine alone will be used, since only here are the numbers sufficiently large. Further, the cases have been divided into five main age groups : -2 years, 2-4 years, 5-9 years, 10-14 years and 15 years and over. Finally, the analysis has been based upon two selective criteria : first, the total dosage used in the assessment is that given to the cases during the first 4 days after admission : and second, the analysis is confined to cases which survived 4 days in hospital. (In all groups those who died prior to the end of the four-day period would of necessity get less of the drugs than those who survived ; this would obviously add to the mortality in the lower dosage group.) These cases have, therefore, been divided into three or more groups according to whether or not they received amounts of drug less than, equal to, or in excess of, that suggested by Banks (1939). The results of this analysis are given in Table VIII. The Table shows that all who died within 24 hours of admission received small amounts of the drug : in the under 2 years and 2-4 years age groups no less than 6 and 9 per cent. respectively of the cases died within 24 hours of

TABLE VIII

RESULTS IN RESPECT OF DOSAGE AT CERTAIN AGE GROUPS
SULPHAPYRIDINE GROUP ONLY

AGE GROUP IN YEARS		AMOUNT OF SULPHAPYRIDINE GIVEN IN FIRST 4 DAYS—DOSAGE IN GRAMMES										Sub- Total	Un- Stated	40+	35-40	30-35	25-30	20-25	15-20	10-15	0-10	Grand Total
		0-10	10-15	15-20	20-25	25-30	30-35	35-40	40+	Un- Stated	Sub- Total											
Under 2	Cases—Total	176	126	(15+)						2	366											
	Cases surviving 4 days	130	121	59						—	310											
	Percentage Mortality under 24 hrs.	5.68	0	0						2/2	3.28											
	after 24 hrs.	28.98	12.70	6.5						—	19.40											
2-4	Cases—Total	11.54	9.09	1.7						—	8.71											
	Cases surviving 4 days		(0-15)	57	(20+)					1	230											
	Percentage Mortality under 24 hrs.		121	52	51					—	182											
	after 24 hrs.		82	0	48					1/1	5.22											
5-9	Cases—Total		9.09	0	0					—	19.57											
	Cases surviving 4 days		24.79	17.5	9.8					—	4.95											
	Percentage Mortality under 24 hrs.		2.4	9.6	4					—												
	after 24 hrs.									—												
10-14	Cases—Total		(0-20)	66	41	12	(30+)			—	132											1468
	Cases surviving 4 days		56	56	38	12	13			—	119											1284
	Percentage Mortality under 24 hrs.		1.5	1.5	0	0	0			—	0.76											2.793
	after 24 hrs.		13.6	13.6	7.3	0	0			—	9.09											14.373
15+	Cases—Total		0	0	0	0	0			—	0											5.296
	Cases surviving 4 days		(0-25)	37	37	14	14	(35+)		—	93											
	Percentage Mortality under 24 hrs.		35	35	28	28	28	38		—	91											
	after 24 hrs.		0	0	0	0	0	0		—	0											
15+	Cases—Total				5	0	0	0		—	2.2											
	Cases surviving 4 days				0	0	0	0		—	0											
	Percentage Mortality under 24 hrs.				0	0	0	0		—	0											
	after 24 hrs.				0	0	0	0		—	0											
15+	Cases—Total				(40+)						647											
	Cases surviving 4 days				98						582											
	Percentage Mortality under 24 hrs.				97						2.473											
	after 24 hrs.				0						12.519											
15+	Cases—Total				10.2						5.50											
	Cases surviving 4 days				9.3																	
	Percentage Mortality under 24 hrs.																					
	after 24 hrs.																					

admission. If only those cases who survived 4 days are considered, some curious discrepancies are encountered. For, although in the age group under 2 years there is a decline in the fatality rate as the dosage increases, such a clear association between dosage and outcome is not seen in the other age groups. In the cases between 2 and 4 years the lowest fatality rate was encountered in those who received the smallest amount of drug; while in those over the age of 15 years the lowest fatality rate was encountered in those who received medium dosage. It is difficult to account for these variations, for the total number of cases in each dose subdivision is reasonably large: it would have been expected that errors due to chance distribution would have been eliminated.

In none of the other treatment groups is the number large enough to permit such minute subdivision. It has already been pointed out that the cases which received combined treatment with serum and sulphonamides were given a slightly lower dosage of the drugs.

We fully realise that the method of analysis adopted, entailing the selection of a particular group of cases, namely, those who survived a period of days in hospital, is open to criticism. Nevertheless, it does secure a series of cases which are wholly comparable in respect of the amount of drug which they were given during this period. Without a much more full analysis of the records it is only possible to draw the broad conclusion that a time has not yet been reached when it is possible to be dogmatic in regard to the optimum dosage. The figures in the Table indeed suggest that in this series the optimum doses for the different age groups are somewhat in excess of those prescribed by Banks; they show, further, that rather more than half of the cases received a dosage in the first four days equal to or greater than that which he has advocated. The high fatality rate encountered in this Scottish series, compared with that reported by Banks, can scarcely be ascribed to inadequacy of dosage, and suggests either that the series contains a greater proportion of fulminant cases, or that the disease, as seen in Scotland, during the epidemic period, was of a more virulent nature than that encountered in the South of England.

DISCUSSION

It is clear from the results tabulated that the introduction of the sulphonamide group of drugs has caused a marked reduction in the mortality from cerebro-spinal fever. The discussion of these results may best be centred round four main points.

(a) Effect of Age.

Clearly, age remains of great importance in the prognosis of this disease: the main mortality now falls on those under the age of 2 years and over the age of 35 years. This finding itself is of some importance for it shows that the problem of the treatment of cerebro-spinal fever is not yet completely solved. It may be argued that the inhibitory effect of the sulphonamide drugs upon the meningococcus is not likely to be dependent upon the age of the patient. Such a contention would suggest that there must be some factor in the disease-process at these ages which prevents the complete success of chemotherapy. It may be noted that in pneumonia too a relative lack of success with sulphonamides has been found in the older age groups (Anderson, 1943). There is apparently a factor involved in effective chemotherapy quite apart from the mere exhibition of the drug.

(b) The Effect of Different Methods of Treatment.

There are practically no clinical therapeutic trials of the sulphonamides which permit a comparison between the effects of the different drugs. For such a comparison to be accurate it is essential that the drugs be administered during the same period of time to cases of a disease chosen by some method, such as an alternating one. The figures in the present report are no more accurate in this respect than are others: clearly an undue proportion of the cases received one drug only—namely, sulphapyridine. So far as the fatality rates and the rapidity of cure as

judged by length of stay in hospital are concerned, sulphanilamide not only is no less effective than the other two, but even produces better results. We would not be prepared, on the strength of the present evidence, to rank the drugs in any "order of preference": but we would go so far as to assert that the results certainly do not indicate that either sulphapyridine or sulphathiazole is a more "active" drug than sulphanilamide in this disease. In only one respect do we see an advantage in using either of the former drugs, namely, in the possibly prophylactic effect in regard to the occurrence of pneumonia.

The failure of the combination of sulphonamides and specific serums or antitoxins must (like age) be regarded as an important finding. Theoretically one would at least have expected the results to be as good as those obtained with the drugs alone. It has already been pointed out that, on the average, the dose of drug which this group obtained was slightly less than that of the sulphonamides-only group. It might also be suggested that this method of treatment was used for particularly severe cases. Against this is the finding that the number of deaths within 24 hours of admission was not appreciably high in this treatment group. We are tempted to conclude that combined treatment was in fact less effective; and to suggest as a possible cause that the serum (which in the main was given intrathecally) may have produced an aseptic irritation of the meninges which lowered their resistance. In the light of the findings in the present study we would advise that combined treatment should not be given.

(c) The Incidence of Complications.

The complicated case rate is high. This might well be expected in a disease of such known severity: especially since the chance of recovery has so much improved that cases may now live long enough to develop complications which were previously not frequently encountered. Even although the incidence of relapse is low its occurrence must always be held in mind; rise of temperature in convalescence should be an indication for lumbar puncture in order that treatment may be immediately restarted. Little can be said in regard to the permanence of the paralytic complications for, in most of the centres, follow-up studies were not conducted. In a proportion of the cases, however, the nerve lesion had cleared up before dismissal from hospital. The infective processes which developed were of a varied nature. Some of them, it may be surmised, were due to cross infection with different pathogenic organisms. The occurrence of such complications forms, as we have said, a reasonable argument for advising the administration of a sulphonamide with a wider range than sulphanilamide.

(d) The Dose of the Drugs.

The present analysis in regard to this question must be regarded as not entirely adequate. It does suggest that much remains to be discovered before a dogmatic statement can be made. It seems reasonable to say that, since the low fatality rate would not have occurred without the administration of a sulphonamide drug, a certain amount of those drugs must be introduced. On the basis of experimental work it would seem that a higher dosage is likely to be more beneficial than a lower one. But the present examination does not suggest a direct correlation between the amount of drug given during the first 4 days, and the final outcome, in those cases who survived 4 days. The question demands further study.

SUMMARY

1. The natural behaviour of cerebro-spinal fever in Scotland during the last forty years is briefly discussed.
2. The records of 2223 cases of this disease occurring in Scotland between 1936 and 1941 are analysed in respect of the method of specific treatment employed (none, serum alone, sulphanilamide, sulphapyridine, sulphathiazole, miscellaneous sulphonamide drugs and sulphonamides + serum or antitoxin), the age and

sex, the duration in days of illness prior to admission, the duration in days of stay in hospital and the occurrence of complications.

3. The use of the sulphonamide drugs has caused a reduction in the fatality rate to 16.7 per cent.
4. Mortality is closely associated with age, the maximal rates being found under 2 years and over 35 years.
5. A comparison between the three main sulphonamide drugs (sulphanilamide, sulphapyridine and sulphathiazole) does not suggest that any one possesses clear advantages over the other.
6. Although a wide variety of complications was encountered no single complication was observed with great frequency. The importance of pneumonia as a cause of death is emphasised.
7. The present analysis does not permit a dogmatic statement in respect of the optimum amount of drug which should be employed.
8. With the sulphonamide drugs between 70 and 80 per cent. of the cases are clinically cured within a period of 4 weeks.
9. Although the sulphonamides seem equally effective when given during any part of the first week of illness, institution of treatment should nevertheless be prompt.

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